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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,593	12/05/2001	Katherine S. Bowdish	1087-2	3532

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EXAMINER

HELMS, LARRY RONALD

ART UNIT PAPER NUMBER

1642

DATE MAILED: 02/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/006,593

Applicant(s)

BOWDISH ET AL.

Examiner

Larry R. Helms

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 November 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23, 36, 44, 45, 85-92 and 96-99 is/are pending in the application.
- 4a) Of the above claim(s) 17, 18, 20, 21, 91 and 92 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-16, 19, 22-23, 36, 44-45, 85-90, 96-99 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. 6) ☐ Other: _____

DETAILED ACTION

1. Claims 24-35, 37-43, 46-84, 93-95 have been canceled.

Claims 96-99 have been added.

Claims 1, 4, 12, 14-18, 20-21, 45, 85-87, 91-92 have been amended.

2. It is noted that in the response to the restriction requirement that an election of SEQ ID NO:2 was elected.

The response filed 11/24/03 states that claim 18 has been amended to recite comprising SEQ ID NO:1 and therefore embraces SEQ ID NO:2 which is essentially SEQ ID NO:1 having an additional amino acid, proline at one end and claims 20, 21, 91, and 92 claims at least one sequence specifically recited therein eg SEQ ID NO:39 which is SEQ ID NO:2 plus additional amino acids. In response to this argument, SEQ ID NO:2 was elected and this is the only species examined. The additional sequences in SEQ ID NO:39 are different as well as SEQ ID NO:1 which is different from SEQ ID NO:2. therefore only SEQ ID NO:2 is examined.

3. Claims 17-18, 20-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

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5. The following Office Action contains NEW GROUNDS of rejection.
6. Claims 1-16, 19, 22-23, 36, 44-45, 85-90 and newly submitted claims 96-99 are under examination.

Information Disclosure Statement

7. The Information Disclosure Statement filed 7/19/02 has been considered in part. All US Patents listed on the IDS have been considered, however, all other references were not considered because copies of the references were not in the file. The examiner apologizes for any inconvenience but requests that copies of the references be supplied and the references will be considered at that time.

Rejections Withdrawn

8. The rejection of claims 1-16, 19, 22-23, 36, 44-45, 85-90 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

Response to Arguments

9. The rejection of claims 1-16, 19, 22-23, 36, 44-45, 85-90 and newly submitted claims 96-99 under 35 U.S.C. 112, first paragraph is maintained.

The response filed 11/24/03 has been carefully considered but is deemed not to be persuasive. The response states that the specification provides a detailed description of how to use antibodies prepared in accordance with the disclosure (see page 12 of response). In response to this argument, the claims still encompass immunoglobulins that have a TPO or EPO mimetic added to the CDR and the molecule does not need to bind EPO or TPO receptors.

10. The rejection of claims 1-16, 19, 22-23, 36, 44-45, 85-90 and newly added claims 96-99 under 35 U.S.C. 103(a) as being unpatentable over Barbas et al [a] (WO 94/18221, published 8/94) and further in view of Dower et al (WO 96/40750, published 12/96) and Barbas et al [b] (PNAS 92:2529-2533, 1995) and as evidenced by Helms et al (Protein Science 4:2073-2081, 1995) is maintained.

The response filed 11/24/03 has been carefully considered but is deemed not to be persuasive. The response seems to argue initially the references separately in stating that Barbas PCT does not teach replacing a CDR with a TPO mimetic of SEQ ID NO:2 (see page 13) and that Barbas PCT generic definition of binding sites encompasses millions of polypeptides and none of the specifically listed material provides motivation to incorporate a TPO or EPO mimetic (see page 14-15). The response argues that Dower fails to disclose incorporating a TPO or EPO mimetic in an immunoglobulin or a flanking sequence (see page 15-16) and Dower is limited to low molecular peptides and does not suggest incorporation into an immunoglobulin (see page 16) and the rejection is clearly an impermissible hindsight reconstruction (see page 17).

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In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. In *re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In *re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In addition, Barbas PCT clearly teach insertion of peptides into CDRs for binding and therapy and to produce peptides that are flanked by amino acids to produce conformationally constrained peptides to enhance binding (see page 84) and Dower clearly teach peptides that bind to TPO receptor for therapy, which comprise SEQ ID NO:2 without the proline at the C terminus, and the peptides can be constrained such as by adding cysteines to cyclize them for better affinity and binding (see Table 9). thus, it would have been obvious to use the peptides of Dower in the methods of Barbas.

The response then states that turning now to claim 44, nowhere in Barbas PCT does it teach or suggest a peptide flanked by a proline at the C-terminus of the peptide

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and the addition of the proline extension provides an unexpected result (see page 180 and Dower does not teach flanking with structural constraints (see page 19 of response). In response to this argument, Barbas clearly teaches constrains to the peptides for presentation by adding additional amino acids at the ends of the peptides by for example cysteines for cyclization and as evidenced by Helms et al PRO residues constrain the conformation of the peptides in immunoglobulin scaffold and as such it was known in the art that PRO residues constrain the conformation of the peptides and would have been obvious to add to the peptides for conformation. In addition, Dower et al does teach flanking sequences for constrained peptides as Dower teach adding cysteins to the ends for cyclization and constrains for the peptide for better affinity.

The response further states that Dower and Barbas PCT do not teach flanking sequences with only two amino acids (see page 20 of response). In response to this argument, Barbas PCT teach a binding site with 5' and 3' terminal nucleotides having 6-50 nucleotides (see page 31). As such 6 nucleotides would encode 2 amino acids, therefore two flanking amino acids are taught in Barbas PCT.

Conclusion

11. No claim is allowed.
12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the

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Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879



LARRY R. HELMS, PH.D.
PRIMARY EXAMINER